

# The association of new-onset diabetes mellitus and medical therapy for benign prostatic hyperplasia: A population-based study

CUA PRIZE ESSAY



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## Abstract

**Introduction:** Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms are highly prevalent in the aging male. Similarly, the prevalence of metabolic syndrome is increasing worldwide, with mounting evidence that these two common conditions share more than age as a predisposing factor. The objective of this study was to determine if medical management of BPH is associated with an increased risk of new-onset diabetes mellitus (DM) in routine care.

**Methods:** This population-based, retrospective cohort study expands on a parent study of linked administrative databases identifying patients diagnosed and treated for BPH between 2005 and 2015. The primary outcome of this secondary analysis was a new diagnosis of DM after the index date of BPH diagnosis. Covariates included age, dyslipidemia, hypertension, and vascular diseases. A Cox proportional hazards regression model was used for inferential statistical analysis.

**Results:** A total 129 223 men were identified with a BPH diagnosis and no prior history of DM. Of those men, 6390 (5%) were exposed to 5- $\alpha$ -reductase inhibitor (5-ARI), 39 592 (31%) exposed to alpha-blocker (AB), and 30 545 (24%) exposed to combination therapy. Compared to those men with no BPH medication use, those exposed to drugs had an increased risk of new DM. Men treated with combination therapy of 5-ARI and AB (hazard ratio [HR] 1.30, 95% confidence interval [CI] 1.25–1.35), 5-ARI monotherapy (HR 1.25, 95% CI 1.17–1.34), or AB monotherapy (HR 1.17, 95% CI 1.13–1.22) all were at higher risk of new DM diagnosis after adjusting for important covariates. When calculating the risk of a new diabetes diagnosis measured from the start of drug exposure, men treated with 5-ARIs had an increased risk of DM compared to AB monotherapy as the reference, with HR 1.12 (95% CI 1.03–1.21) for 5-ARI monotherapy and HR 1.20 (95% CI 1.14–1.25) for combination therapy.

**Conclusions:** In this large, long-term, retrospective study of men with a BPH diagnosis in routine practice, the risk of a new diagnosis of DM was greater in patients receiving medical management

compared to controls. This modest but significant increased risk was highest in men treated with any 5-ARIs, in combination as well as monotherapy, compared to the ABs.

## Introduction

Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms are highly prevalent in the aging male, resulting in a significant public health burden, which globally affects approximately 50% of men age 65 or older.<sup>1,2</sup> Similarly, the prevalence of metabolic syndrome, a cluster medical disorder including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension, is increasing worldwide, with almost 50% of men over age 60 in the United States meeting diagnostic criteria.<sup>2,3</sup> There is increasing evidence that these two common conditions share more than age as a predisposing factor.<sup>4</sup> Epidemiological and pre-clinical studies suggest that metabolic syndrome, or its individual components, are associated with the development of urinary symptoms, increase in prostate growth, and progression of BPH.<sup>5,6</sup>

These previous findings have generated a hypothesis of a causal relationship between metabolic syndrome and the development of BPH, with biological rationale including sex steroid alterations, increased sympathetic tone, and low-grade inflammation.<sup>7</sup> Perhaps more intriguingly, these patients may share similar metabolic abnormalities of defective insulin-mediated glucose uptake and secondary hyperinsulinemia, with subsequent stimulation of prostate growth by insulin and other related trophic factors. However, this mounting evidence connecting type 2 diabetes mellitus (DM) and risk of BPH is complicated by recent pre-clinical and clinical studies linking the development of DM to the medications used for the management of BPH, specifically the 5- $\alpha$  reductase inhibitors (5-ARI).<sup>8–10</sup>

Both alpha-blockers (AB) and 5-ARIs have been proven to be effective treatment options for BPH with high-quality evidence<sup>2</sup> and the use of 5-ARI for BPH has steadily increased.

Although 5 $\alpha$ -reductase 2 is mostly expressed in prostate and skin (blocked by finasteride and dutasteride), 5 $\alpha$ -reductase 1 (blocked by dutasteride) is also active in metabolic tissues, such as the liver and adipose tissue.<sup>11</sup> Androgens promote normal glucose utilization by stimulating glucose uptake, glycolysis, and mitochondrial oxidative phosphorylation.<sup>12</sup> Despite large prospective trials of 5-ARIs for BPH not demonstrating any safety signal for DM,<sup>13,14</sup> a recent non-randomized cohort study suggested that longer-term dutasteride use was associated with an imbalance of metabolic function, lower testosterone levels, increased HbA1c, and altered lipid profiles.<sup>9</sup> However, larger observational studies investigating the association between BPH medication use and new type 2 DM diagnosis have demonstrated inconsistent results.<sup>15,16</sup>

Although such observational studies are helpful to explore relatively uncommon associations given their large number of men exposed, difficulties in interpretation arise from residual confounding. Indeed, it is problematic controlling for confounding within studies of chronic conditions such as BPH, as there is evidence that certain risk factors are more prevalent among patients starting drug treatment for BPH as compared to controls.<sup>1,17</sup> The objective of the present study was to determine if medical management was associated with an increased risk of new-onset DM in males with a BPH diagnosis and medication use in routine care.

## Methods

This population-based, retrospective cohort study explores the risks of developing subsequent DM after a diagnosis of BPH, specifically exploring the effect of medication use with 5-ARIs and ABs. The present study expands on a parent study (secondary analysis) of linked administrative databases identifying patients diagnosed with BPH and subsequent diagnosis of congestive heart failure in Ontario, Canada between January 1, 2005 and December 31, 2015.<sup>1</sup> The maximum followup date was December 31, 2018. Males aged 66 years or older with a diagnosis of BPH were initially included in the study, as prescription information is routinely captured for those men over 65. International Statistical Classification of Diseases and Related Health Problems (ICD) codes, both ICD-9 and ICD-10, were used to identify the diagnosis of BPH, as the timeline included both versions of ICD classification. Exclusion criteria in the parent study included absence of valid Ontario health-care, death at index, cardiac failure within the last five years of index date of BPH diagnosis, and those previously diagnosed with prostate cancer. Patients that used 5-ARI or AB within one year of diagnosis were excluded and, for this secondary analysis, patients with a previous diagnosis of DM were also excluded. The Queen's University Health Sciences and Affiliated Hospitals Research Ethics Board approved this study.

Administrative databases used were all linked through the Institute of Clinical Evaluative Sciences (ICES). Each database

is routinely used for research purposes and has been previously validated.<sup>18</sup> Linked records included those with the Discharge Abstract Database, Ontario Health Insurance Plan (OHIP) physician claims-database, the Ontario Drug Benefit plan, Registered Persons Database and Same Day Surgery database. The accuracy of these databases in terms of quality and coding has been previously discussed.<sup>19</sup> Statistics Canada's 2016 census data was used to infer socio-economic status (SES) by linking postal code of residence to the mean household income by dissemination area.

The primary outcome of this secondary analysis was a new diagnosis of DM after the index date of BPH diagnosis. In order to account for sampling biases based on baseline risks for DM, men included in the study were then categorized based on their exposure to medical treatment. The control was men who received no treatment, and this was compared to 5-ARI monotherapy, AB monotherapy, and combination therapy of 5-ARI and AB. 5-ARI included both finasteride and dutasteride, and AB included both selective and non-selective medications. Exposure time to medication (5-ARIs and/or ABs) was listed as number of days of medication use. Covariates that were considered a priori included age, dyslipidemia, hypertension, and vascular disease encompassing previous diagnosis of myocardial infarction, peripheral vascular disease, or cerebral vascular disease. An overall score of comorbidities, using the John Hopkins' Aggregated Diagnosis Groups (ADGs) was used.

Descriptive statistics were used for baseline characteristics describing the cohorts based on medications used for BPH. A Cox proportional hazards regression model was used for inferential statistical analysis. The associated risk of subsequent type 2 DM following the initiation of BPH medical therapy (5-ARI and AB) was evaluated using univariate, as well as multivariable competing risk analyses adjusted for all described covariates. Each patient's index date was first diagnosis of BPH. To account for immortal time bias, subsequent analysis included only those prescribed medications, and the risk of DM was then measured from the start of first drug exposure. Statistical significance was set at a two-sided p-value of <0.05. Data were analyzed using SAS Stat 14.3.

## Results

There were 282 462 men included in the study over the age of 66 with a diagnosis of BPH. After exclusions, 129 223 men met the study criteria. Of those men included with a BPH diagnosis, 52 696 had no evidence of either AB or 5-ARI prescriptions, whereas 6390 (5%) were exposed to 5-ARI, 39 592 (31%) exposed to AB, and 30 545 (24%) exposed to combination therapy. The median age of the cohort was 73 years and other baseline characteristics between men based on BPH medication use were similar, including past

**Table 1. Baseline characteristics of men diagnosed with BPH in Ontario between 2005 and 2015 according to BPH drug exposure**

	No medications	5-ARI	AB	Both 5-ARI and AB
No. of patients	52 696	6390	39 592	30 545
Age, years				
Mean $\pm$ SD	73.88 $\pm$ 6.61	74.20 $\pm$ 6.33	74.23 $\pm$ 6.47	74.05 $\pm$ 6.20
Median (IQR)	72 (68–78)	73 (69–78)	73 (69–78)	73 (69–78)
66–70, n (%)	20 821 (40%)	2265 (35%)	13 995 (35%)	10 781 (35%)
71–75, n (%)	13 553 (26%)	1756 (27%)	10 983 (28%)	8621 (28%)
76–80, n (%)	9166 (17%)	1262 (20%)	7525 (19%)	6191 (20%)
81+, n (%)	9156 (17%)	1107 (17%)	7089 (18%)	4952 (16%)
Vascular diseases, n (%)	3330 (6%)	386 (6%)	2661 (7%)	1748 (6%)
History of dyslipidemia, n (%)	3531 (7%)	422 (7%)	3018 (8%)	2081 (7%)
History of hypertension, n (%)	31 704 (60%)	3987 (62%)	25 174 (64%)	19 291 (63%)
History of chronic ischemic heart disease, n (%)	5217 (10%)	631 (10%)	4301 (11%)	2918 (10%)
No. Aggregate Diagnosis Group (ADG)				
Mean $\pm$ SD	10.55 $\pm$ 4.23	10.46 $\pm$ 4.21	11.02 $\pm$ 4.21	10.76 $\pm$ 4.28
Median (IQR)	11 (8–13)	10 (7–13)	11 (8–14)	11 (8–14)
0–6 ADGs, n (%)	9432 (18%)	1143 (18%)	5821 (15%)	4992 (16%)
7–9 ADGs, n (%)	12 039 (23%)	1490 (23%)	8268 (21%)	6387 (21%)
10–11 ADGs, n (%)	9499 (18%)	1162 (18%)	7126 (18%)	5554 (18%)
12–13 ADGs, n (%)	8589 (16%)	1033 (16%)	7079 (18%)	5357 (18%)
14+ ADGs, n (%)	13 137 (25%)	1562 (24%)	11 298 (29%)	8255 (27%)
No. major ADG, n (%)				
0 ADGs	8684 (16%)	1089 (17%)	5787 (15%)	4815 (16%)
1 ADGs	13 599 (26%)	1713 (27%)	9599 (24%)	7975 (26%)
2 ADGs	12 497 (24%)	1547 (24%)	9903 (25%)	7703 (25%)
3 ADGs	8907 (17%)	1046 (16%)	7269 (18%)	5340 (17%)
4 + ADGs	9009 (17%)	995 (16%)	7034 (18%)	4712 (15%)
Total days of 5-ARI exposure				
Mean $\pm$ SD	NA	1,329 $\pm$ 1,222	NA	1168 $\pm$ 1140
Median (IQR)	NA	967 (240–2230)	NA	766 (210–1861)
Total days of alpha-blocker exposure				
Mean $\pm$ SD	NA	NA	886 $\pm$ 065	1372 $\pm$ 1245
Median (IQR)	NA	NA	410 (90–1358)	1019 (300–2157)
Total days of exposure concurrent use of 5-ARI and AB				
Mean $\pm$ SD	NA	NA	NA	1145 $\pm$ 1185
Median (IQR)	NA	NA	NA	702 (150–1861)
Days with 5-ARI/days on study				
Mean $\pm$ SD	NA	0.89 $\pm$ 0.19	NA	0.86 $\pm$ 0.22
Median (IQR)	NA	1 (1–1)	NA	1 (1–1)
Days with AB/days on study				
Mean $\pm$ SD	NA	NA	0.82 $\pm$ 0.27	0.79 $\pm$ 0.28
Median (IQR)	NA	NA	1 (1–1)	1 (1–1)
5-ARI compliance	0 (0%)	4449 (70%)	0 (0%)	20 574 (67%)
Alpha-blocker compliance	0 (0%)	0 (0%)	20 550 (52%)	21 800 (71%)

Percentages presented are column percentages. AB: alpha-blockers; 5-ARI: 5-alpha-reductase inhibitor; BPH: benign prostatic hyperplasia; IQR: interquartile range; SD: standard deviation.

history of cardiac disease, hypertension, and dyslipidemia (Table 1). The total number of days on drug and measures of continuous use are also outlined in Table 1. This demonstrated that those on AB monotherapy had a median number

of 410 days of exposure (90–1358), which was similar to other BPH medication exposure groups.

Men prescribed 5-ARI monotherapy, AB monotherapy, or combination therapy had an increased risk of DM in

**Table 2. Sub-distributional hazard ratios for new diabetes mellitus diagnosis**

	Unadjusted			Adjusted	
	Rate	HR ( $\pm$ 95% CI)	p	HR ( $\pm$ 95% CI)	p
5-ARI exposure	14.15	1.26 (1.17–1.35)	<0.001	1.25 (1.17–1.34)	<0.001
Alpha blocker	12.92	1.19 (1.15–1.24)		1.17 (1.13–1.22)	
Both 5-ARI and alpha blocker	14.83	1.32 (1.27–1.37)		1.30 (1.25–1.35)	
No medications	10.74	Ref		Ref	
Age at index date					
66–70	13.92	Ref	<0.001	Ref	<0.001
71–75	13.49	0.95 (0.91–0.98)		0.91 (0.87–0.94)	
76–80	12.17	0.85 (0.81–0.88)		0.78 (0.75–0.82)	
81+	8.51	0.58 (0.55–0.61)		0.53 (0.50–0.56)	
History of dyslipidemia					
No	12.31	Ref	<0.001	Ref	<0.001
Yes	15.62	1.31 (1.24–1.38)		1.16 (1.10–1.24)	
History of hypertension					
No	10.00	Ref	<0.001	Ref	<0.001
Yes	14.10	1.45 (1.40–1.50)		1.48 (1.43–1.53)	
History of chronic ischemic heart disease					
No	12.30	Ref	<0.001	Ref	<0.001
Yes	14.70	1.20 (1.15–1.26)		1.13 (1.07–1.19)	
# major ADGs					
0 ADGs	11.88	Ref	0.03	Ref	0.24
1 ADGs	12.70	1.06 (1.01–1.11)		1.03 (0.98–1.08)	
2 ADGs	12.62	1.04 (0.99–1.10)		1.01 (0.96–1.06)	
3 ADGs	13.06	1.08 (1.02–1.14)		1.04 (0.99–1.10)	
4 + ADGs	12.26	1.01 (0.95–1.07)		0.99 (0.94–1.05)	
Socio-economic status					
1–Lowest	13.79	Ref	<0.001	Ref	<0.001
2	13.20	0.95 (0.91–1.00)		0.94 (0.90–0.99)	
3	12.97	0.94 (0.89–0.99)		0.93 (0.88–0.97)	
4	12.39	0.89 (0.85–0.93)		0.87 (0.83–0.92)	
5–Highest	10.89	0.77 (0.74–0.81)		0.77 (0.73–0.81)	

Adjusted for all covariates shown in Cox proportional hazards model. Time starts from benign prostatic hyperplasia diagnosis. ADG: Aggregate Diagnosis Group; 5-ARI: 5-alpha-reductase inhibitor; CI: confidence interval; HR: hazard ratio.

comparison to those with a BPH diagnosis and no exposure to medical therapy. Table 2 represents both unadjusted and adjusted models of variables associated with a new-onset DM. As expected, this multivariable analysis shows age, SES, as well as comorbidities linked with metabolic syndrome, to be associated with the primary outcome. Compared to those men with no history of BPH medication use, those exposed to AB had an increased risk of new DM, with a hazard ratio (HR) of 1.17 (95% confidence interval [CI] 1.13–1.22). Similarly, those exposed to 5-ARI monotherapy (HR 1.25, 95% CI 1.17–1.34) and combination therapy (HR 1.30, 95% CI 1.25–1.35) were both at higher risk of a new DM diagnosis after adjusting for important covariates.

To address a possible immortal time bias for those initiating BPH medications, a multivariable competing risk analysis was performed on only those patients exposed to BPH medical therapy (n=76 527) starting at first drug exposure. Men treated

with 5-ARIs had an increased risk of DM compared to AB monotherapy as the reference, with HR 1.12 (95% CI 1.03–1.21) for 5-ARI monotherapy and HR 1.20 (95% CI 1.14–1.25) for combination therapy (Table 3). The cumulative incidence function estimate was adjusted for age, dyslipidemia, hypertension, chronic ischemic heart disease, SES, and major ADG and further demonstrated the increased risk of new DM with 5-ARI exposure compared to AB monotherapy (Fig. 1).

Subsequent sensitivity analyses were performed examining the different BPH medication types demonstrating no significant difference in the primary outcome between selective and non-selective ABs and no difference between finasteride (type 1 5-ARI) and dutasteride (type 1 and 2 5-ARI) in adjusted analysis (data not shown). Any 5-ARI exposure (monotherapy or combination) had an 18% increased risk of a new DM diagnosis in adjusted analysis compared to AB monotherapy (HR 1.18, 95% CI 1.13–1.24).

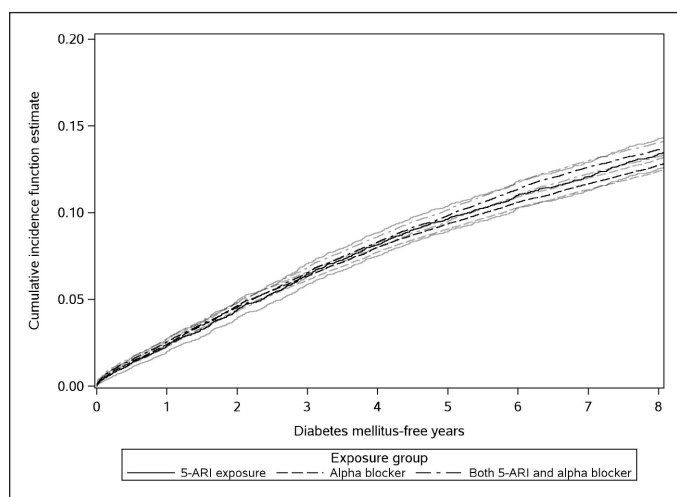


**Table 3. Sub-distributional hazard ratios for new diabetes mellitus diagnosis in men initiating medical therapy for BPH**

	Reference	Adjusted model	
		HR ( $\pm$ 95% CI)	p
5-ARI exposure	Alpha-blocker	1.12 (1.028–1.214)	<0.001
Both 5-ARI and alpha blocker	Alpha-blocker	1.20 (1.142–1.253)	<0.001
Any 5-ARI (monotherapy & combination)	Alpha-blocker	1.18 (1.13–1.24)	<0.001
Non-selective alpha-blocker	Selective alpha-blocker	0.94 (0.85–1.04)	0.23
Dutasteride	Finasteride	0.97 (0.82–1.14)	0.72

Adjusted for age, dyslipidemia, hypertension, chronic ischemic heart disease, socio-economic status, major ADG in Cox proportional hazards model. Time starts from first drug exposure. ADG: Aggregate Disease Group; 5-ARI: 5-alpha-reductase inhibitor; BPH: benign prostatic hyperplasia; CI: confidence interval; HR: hazard ratio.

There was a significant effect of time (unit=one day) on any 5-ARI exposure and a new DM diagnosis when analyzed as a continuous variable with at least four years of followup. Because of concern for the assumption of linearity and a desire to determine if there was any threshold of drug exposure on outcome, we also analyzed drug exposure based on different time cutpoints. There was a trend to a lower risk of new DM in adjusted models when exposure was less than one year (HR 0.89, 95% CI 0.78–1.02,  $p=0.09$ ), however, analyses investigating other single cutpoints of drug exposure were uninformative. Tertile analysis demonstrated disparate results in that that shortest tertile of drug exposure (less than 603 days) had a 36% decreased risk of DM compared to the second tertile (603–2015 days), with a HR 0.64 (95% CI 0.56–0.74). However, those exposed to the



**Fig. 1.** Cumulative incidence function curve of new diabetes mellitus by exposure group. Adjusted for age, dyslipidemia, hypertension, chronic ischemic heart disease, socio-economic status, and major Aggregated Diagnosis Group. 5-ARI: 5-alpha-reductase inhibitor.

drug for longer periods (greater than 2015 days) also had a decreased risk of new DM in adjusted analysis compared to the second tertile, suggesting either a lack of a clear and measurable causal relationship of dose dependence and the primary outcome, bias introduced by drug discontinuation, or residual confounding in those cohorts of men on 5-ARIs for long time periods.

## Discussion

This study used a large, population-based, retrospective cohort representing all men in the province of Ontario with a diagnosis of BPH in order to determine the potential added burden of commonly prescribed BPH medications, 5-ARI and AB, on a new diagnosis of DM. Several interesting and clinically relevant observations were made.

First, we found that exposure to any BPH medication, 5-ARIs and/or ABs, had a higher rate of new DM diagnosis compared to those men diagnosed with BPH unexposed to these medications. Second, we found that the cumulative incidence of DM was higher in those exposed to 5-ARIs, prescribed either alone or in combination with ABs, compared to ABs alone. These initial results guided subsequent analysis of the cohort to further interrogate the association of DM with 5-ARIs, which remained significant after controlling for key covariates linked to metabolic syndrome. Third, there was no observed difference between finasteride and dutasteride with the primary outcome in adjusted analysis. Finally, there was some signal associating time on 5-ARIs and DM on adjusted analysis, although there was no well-defined time cutpoint, suggesting some complexity of these associations.

The link between BPH and metabolic syndrome, both its components and associated negative cardiovascular outcomes, is intriguing not only because of their equally high prevalence in the aging male but also some potential shared pathophysiology.<sup>5-7</sup> Bourke and Griffin were the first to suggest an association between DM and BPH etiology, based on the higher prevalence of the disease among men subjected to prostatectomy than in the general male population.<sup>20</sup> In 1998, Hammarsten et al published that patients with lower urinary tract symptoms and DM had larger prostate volumes when compared to males without DM.<sup>21</sup> Increasing evidence lends credence to the concept that the associated hyperglycemia and insulin resistance of those men with DM can significantly increase the risks of BPH and the subsequent lower urinary tract symptoms.<sup>22,23</sup> The possible biological mechanisms to bolster these associations include increased sympathetic tone, stimulation of prostate growth by trophic factors, and induction of low-grade oxidative stress and systemic inflammation and, relevant to this study, alterations in sex steroid hormone activity.<sup>7</sup>

Associations have been made between low levels of testosterone and insulin-resistant state, with evidence that sex

steroid hormones may play a causal role in development of insulin resistance and type 2 DM.<sup>24-26</sup> Interventional studies have shown beneficial effects of exogenous testosterone on components of the metabolic syndrome, type 2 DM, and other cardiovascular risk factors, including insulin resistance and high levels of cholesterol.<sup>27</sup> Testosterone is involved in promoting glucose utilization, modulating expression of insulin receptors, positively influencing key enzymes involved in glycolysis and mitochondrial oxidative phosphorylation.<sup>12</sup> Given these findings, it is rational to consider the role of BPH medications, specifically the 5-ARIs, on glucose intolerance and DM.

Of the two isozymes of 5 $\alpha$ -reductase, type 2 predominates in the reproductive tissues, whereas type 1 is also found in the skin, liver, skeletal muscle, and testes.<sup>28</sup> Finasteride effectively inhibits the type 2 isoenzyme, reducing circulating serum concentrations of DHT by approximately 70%, with transient increases in circulating testosterone; dutasteride, as a dual inhibitor, causes greater reduction in serum DHT concentrations, although it is less clear whether this results in important effects on other androgen-responsive tissues. Murine studies have shown 5-ARIs can increase susceptibility to diet-induced obesity, impaired glucose tolerance, and increased incidence of fatty liver.<sup>10</sup> Traish et al recently reported increased blood glucose and glycated hemoglobin A1c after several years of dutasteride treatment.<sup>9</sup>

Large, population-based, epidemiological studies have the potential to be adjunctive to prospective clinical trials and single- or multi-institutional observational studies, given their ability to identify and quantify uncommon outcomes, such as adverse effects, in the general population by avoiding various selection biases. Two previous population-level studies investigating the effect of 5-ARI use and new DM were conflicting.<sup>15,16</sup> Lee et al, using a national research database in Taiwan, reported a lower risk of type 2 DM in men receiving at least 28 days of 5-ARI, although the control group was not well-delineated and the total number of men exposed was low with less fulsome baseline characteristics.<sup>15</sup> On the other hand, a more robust study using the U.K. Clinical Practice Research Datalink evaluating 55 275 men receiving BPH medications did show an increased risk of 5-ARI exposure compared to tamsulosin.<sup>16</sup> Although the authors hypothesized that the association would be greatest for dutasteride, given its dual inhibition of 5- $\alpha$  reductase, both dutasteride and finasteride had higher risks of subsequent DM: HR 1.32 (95% CI 1.08–1.61) and HR 1.26 (95% CI 1.10–1.45), respectively. Although the U.K. dataset contains longitudinal records of more than 500 primary care offices, it only accounts for 7% of the U.K. population and may not be generalizable to the whole population. As well, Wei et al use tamsulosin use as the control group, which could bias the results, as ABs have been shown to improve fasting plasma glucose, insulin, and low-density lipoprotein

cholesterol levels.<sup>29</sup> Finally, the interactions between the ABs and 5-ARIs were not robust, given the low number of men on combination therapy.<sup>16</sup>

This present study incrementally adds to this concept and mirrors many of the findings of the U.K. observational study, with similar effect size of the 5-ARIs on subsequent DM. Importantly, we demonstrate that men who have received medical therapy with either AB or 5-ARI are at higher risk of new-onset DM compared to a control group that has never been exposed. This finding recapitulates previous observations that certain risk factors of metabolic syndrome or cardiovascular disease are more prevalent among patients starting drug treatment for BPH as compared to controls.<sup>1</sup> Also, based on the cumulative incidence function estimates, ABs do not appear to mitigate any increased association of 5-ARI on later DM diagnosis for men on combination therapy.

It is important, however, to consider the current limitations of this study, which include all those of similar population-based investigations, including its retrospective nature and the accuracy of available diagnostic administrative codes. Another limitation of the study is that the population was predominantly Caucasian and certain baseline characteristics, including body mass index and other prostate-specific data (such as size and prostate-specific antigen), were not available and limited our ability to conduct an instrumental variable analysis to explore unmeasured confounders. Furthermore, it is not possible to infer the compliance of BPH medication use as compared to drugs dispensed. Finally, the results exploring the biological plausibility of any association with DM with duration of exposure of 5-ARIs was inconsistent.

## Conclusions

In this large, long-term, retrospective, population-based study of men with a BPH diagnosis, the risk of a new diagnosis of DM was greater in patients receiving medical management compared to controls. This modest but significant increased risk was highest in men treated with any 5-ARIs, in combination and as monotherapy, compared to the ABs. As both BPH and the metabolic syndrome increase with age, it is important to consider this potential increased risk when prescribing these drugs in the context of other risk factors for DM.

**Competing interests:** The authors do not report any competing personal or financial interests related to this work.

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be inferred. Dr. Siemens had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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